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REVIEW ARTICLE

What Can We Learn From the Phenomenon of Preferential Lymph Node Metastasis in Carcinoma?

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Lymph nodes are the most common and earliest site of malignancies arising in epithelia. However, the reason for this pattern of preferential metastasis is not clear. This article reviews features of the metastatic process and lymph node microenvironment which might potentiate lymph node metastases. There is intriguing evidence that preferential lymph node metastasis is due to (1) the efficiency of lymph nodes as filters of the tumor cells which arrive there, and (2) the probability that adhesive interactions, normally governing the generation of different T-cell immune responses, are responsible for this efficiency and may also promote invasion and proliferation of tumor cells in the lymph node. Manipulation of the cytokine environment in a lymph node draining a primary epithelial tumor may alter both the expression of cell adhesion molecules within the node and the subsequent metastatic ability of the tumor cells arriving at it.
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KEY WORDS: preferential lymph node metastasis; primary epithelial tumor; lymphatic environment

At the approaching close of the 20th century, medical and surgical practice have achieved the ability to remove all but the most extraordinary primary malignant cancers. It is metastases from the primary tumor, as opposed to the original tumor, which usually kill the patient, and local regional lymph nodes are the most common and earliest site of metastasis of epithelial tumors [1]. However, the reason for this pattern is not clear. Lymphatics drain primary tumors, but preferential growth of tumor cells is not guaranteed in the first organ filter in most experimental systems. Further, the lymph node's role in the immune response might be expected to result in an especially hostile environment for an arriving tumor cell. In this review, we will attempt to address the phenomenon of preferential nodal metastasis by considering which features of a lymphatic environment might promote the process of metastasis as it is currently understood.

Lymph nodes were first described in 1622 by Gasparo Aselli, who dissected mesentery from dog and observed what we now know to be mesenteric lacteals (vessels with a "milky content" which drained to a central node). The term "lymphatics" was coined in 1653 by Thomas Bartholin and Olof Rudbeck, and was used to describe the "serous vessels" previously described by Aselli. By the end of the 19th century, gross and microscopic details of the lymph node were available. In fact, much of our current understanding of the lymphatic system comes from observations made at that time by Sappey, who portrayed cutaneous lymphatics; Von Recklinghausen, who did extensive descriptive work on lymph capillaries; and Virchow, who described the relationship of the lymph node to metastatic disease [2].

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The modern view is that lymph nodes are secondary centers of immune response—localized concentrations of lymphocytes distributed along lymphatic channels where antigen from the periphery is also concentrated. Lymphocytes within the lymph node are organized into a medulla and a cortex, which are surrounded by a marginal sinus. B lymphocytes are concentrated into primary follicles and germinal centers that are surrounded by collections of T lymphocytes [3]. Specialized postcapillary venules within lymph nodes called high endothelial venules (HEVs) are localized to the area surrounding primary follicles in the cortex and mediate trafficking of lymphocytes from the blood into the lymph node where the lymphocytes respond to antigen presented in the node. HEVs express ligands that direct T lymphocytes to the desired lymph node and B lymphocytes to the nodal follicles [4]. Lymph flow enters the lymph node in the marginal sinus and material is filtered through medullary sinuses and cords of B lymphocytes. The materials drained are routed to efferent vessels where they exit the lymph node and proceed through lymphatic circulation to main collecting ducts and finally anastomose with the vascular system.

Tumor cells initially arrive in the marginal sinus of the lymph nodes as discontinuous embolizations from the primary tumor [5]. In 1860, Virchow described the lymph node as serving a barrier function to the spread of cancer cells in the lymph system [2]. William Halsted's radical mastectomy for breast cancer became the signature cancer operation consciously designed to translate this view into clinical practice. The perception that the lymph node acts as a net capturing the initial dissemination of the cancer remains the conceptual foundation for most surgical procedures labeled "cancer surgery," although modern surgical oncologists now tend to tout superior staging as the only benefit. Clearly, infestation of the local regional lymph nodes by tumor cells provides prognostic information. The presence of even micrometastases in tumor-draining lymph nodes correlates with a poorer prognostic outcome for the patient [6]. In later stages, lymphatics and lymph nodes become clogged with tumor cells and the lymph node can no longer filter the cells. The node becomes an independent tumor and is quite capable of inducing subsequent metastases if it is removed and transplanted to another animal [7]. Although lymph node size is often indicative of infiltration by tumor cells, this is not invariably true. A small node can contain metastases and a large hyperplastic node may be devoid of tumor infiltration [8,9]. Still, with few exceptions, there is no more powerful prognostic indicator for human epithelial malignancy than the presence of tumor cells within a lymph node.

More contemporary orthodoxy views the important prognostic information imparted by local regional lymph node status simply as a reflection of the biologic aggressiveness of the primary tumor. Metastases are *not* thought to occur first via lymphatics (lymphogenous spread) and subsequently via the bloodstream (hematogenous dissemination) once the local regional lymph nodes are overwhelmed. Rather, dissemination is thought to occur synchronously via lymphatics and blood capillaries. Evidence for the accuracy of this perception of how cancer spreads is powerful. Clinical examples of non-lymphatic dissemination abound not only in classes of tumors such as sarcomas, but also in epithelial tumors that frequently do involve local regional lymph nodes, such as node negative colon cancer metastatic to the liver. Experimental demonstrations of tumor cells in local regional lymph nodes following intravascular injections and in venous blood following lymphatic injection also tend to suggest that lymphogenous and hematogenous metastases are not distinctly different from one another [10]. Finally, it appears that tumor cells are shed into the circulation, in proportions related to the vascular cross-sectional area of the tumor after the tumor develops its own blood supply [11]. Increased tumor vascularity in clinical breast cancer correlates with increased lymph node metastases [12]. Consequently, an established nodal metastasis is thought more to reflect what the tumor is capable of elsewhere in the body. As Fisher's aphorism summarizes it: "Lymph nodes are indicators, not instigators of distant disease." This view of cancer spread does not, however, account for what appears to be preferential lymph node metastasis.

The possibility that the lymph node is an initial filter for cells from the primary tumor has enjoyed an intellectual renaissance in the past several years. Injection of isosulfan blue and radiocolloid into the site of the primary tumor followed by biopsy of the first lymph node absorbing the dye, radionucleotide, or both, identifies the lymph node that cells from the primary tumor initially travel to—"sentinel lymph node" [13]. If the sentinel node is clear of disease the rest of the nodal basin draining the tumor site will be free of metastases most of the time, whereas a positive sentinel node will be the only metastatic disease in the nodal basin approximately one third of the time [14]. The dramatic clinical success of this technique in melanoma [15,16] and breast [17] suggests that the pattern of preferential nodal metastasis may be at least partially due to a filtering function of lymph nodes.

However, experimental studies have shown that the site of initial arrest of the tumor cells does not necessarily define the eventual site of metastatic colonies. Rather, the final site of a metastatic tumor results from proliferation of tumor cells and supporting stroma at a particular site. The tissue site is "chosen" based not only on tumor cell adhesion to particular endothelia, but also on responsiveness of certain cancer cells to the growth factors, or the unresponsiveness of these tumor cells to para-

crine growth inhibitors at that site [18,19]. Clinical examples of this phenomenon of preferential metastasis include the predilection of lung cancer for the adrenal gland and melanoma for the submucosa of the small intestine. Examples in rodent tumor models are even more striking and include lung metastasizing tumors whose cells will home to explants of fetal lung placed in ectopic locations [20].

The particular points in the metastatic cascade which might lead to the phenomenon of preferential lymph node metastasis are well described. Tumor cells must separate from the primary tumor mass and invade the microvasculature (capillary and lymphatic) which appears to occur when the primary tumor has developed a blood supply [21]. The tumor cell must subsequently survive in circulation, attach to congenial tissue, and invade the stroma of the organ to which it has adhered [11,22]. Throughout this process, the tumor cells must continuously evade the host defense system and establish a population of cells capable of inducing angiogenesis [21]. Very few tumor cells can accomplish all of the feats necessary for success. Hence, the process is inherently inefficient. Those cells that do typically arise from clonal subpopulations within the primary tumor [23] and some of these subpopulations have predilections for particular organ sites.

Although there is no evidence for the regular generation of subclones of cells in epithelial malignancies that have especial predilection for lymph nodes, it is reasonable to expect a large proportion of tumor cells that detach from a primary tumor to wind up in the lymph node. Interestingly, the destruction of the tumor cells in the lymph node environment does not appear to be as successful as the destruction of the same cells in blood vessels [24]. When tumor cells are injected into rat lymphatics at low doses, more tumor metastases are established there compared to those established through intravenous injection [25].

Cells other than tumor cells which normally arrive in local regional lymph nodes include T and B lymphocytes and professional antigen presenting cells (APC) such as macrophages and dendritic cells. The tantalizing possibility is that tumor cells may use the same mechanisms of migration and adhesion as these immune cells responding to antigen or inflammation. Whereas the lymphocytes arrive predominantly via an endothelium highly specialized for lymphocyte trafficking (HEV), Langerhans/dendritic cells arrive from the mucosa via afferent lymphatics. The migration of Langerhans cells in the mucosa to the lymph node is marked by evolution into a follicular dendritic cell with substantial reductions in the expression of the adhesion molecule E-cadherin and parallel upregulation of ICAM-1 expression [26]. The migration of these cells to the lymph node can be blocked by a monoclonal antibody against an α-6 integrin receptor for laminin but cannot be blocked by antibodies directed against integrin receptors for other matrix molecules such as fibronectin [27].

Downregulation of adhesion molecules such as E-cadherin molecules is a common finding in tumor cells that do spread to lymph nodes [28] and probably simply reflects the cells' success in the first step of the metastatic cascade: detachment from the primary tumor. Nevertheless, positive adhesive interaction with other cells and with matrix is a critical step in the establishment of a metastatic focus. In this respect, the importance of the adhesive interaction of dendritic cells with laminin in their successful "colonization" of local regional lymph nodes is reminiscent of the role laminin binding plays in promoting metastasis for a wide variety of tumor cells in sites other than lymph nodes [11,29,30]. Although typically found in basement membranes, laminin also appears to be sequestered in the luminal glycocalyx of lymph node HEVs, perhaps contributing to the efficiency of HEVs in lymphocyte trafficking [4]. Even lymphocyte attachment and invasion of non-nodal sites of immune response can be partially blocked by inhibition of laminin binding [31].

Another matrix molecule that may play an important role in lymph node metastasis is hyaluronate. Hyaluronate is a matrix glycosaminoglycan found in abundance wherever new tissue is being formed and cell motility is increased. The evidence that hyaluronate may be important in lymph node metastasis is derived chiefly from the fact that it is the main, but not the only, ligand for the adhesion molecule CD44 [32,33]. CD44 modulates cell-matrix interactions, presentation of growth factors and cytokines, and has a role in mediating lymphocytes homing to HEV in Peyer's patches and lymph nodes [34]. T lymphocytes that have been activated by immune stimuli upregulate CD44 isoforms expressing variant exons [35]. Although CD44 does not appear to play a particularly important role in the migration of Langerhans/dendritic cells from the periphery to the lymph node [26], many metastatic tumor cells express high levels of either CD44 or one of its variants [34]. In one model system of a rat pancreatic carcinoma, a CD44 splice variant isoform that is normally associated with lymphocyte activation confers the ability to metastasize to lymph node particularly [36]. Adhesive interactions of immune cells with other cells and with matrix in vivo develop more fully and firmly during an initial rolling encounter [37] and lymphocytes in lymph nodes roll along a reticular network. This behavior appears to be mediated by CD44 and hyaluronate, which coats the reticular infrastructure of the lymph node and tonsil [38]. However, as is true for laminin, there is otherwise no direct evidence for increased concentrations of hyaluronate in the lymph node matrix.

There is evidence for increased adhesion of lymph node metastasizing melanoma cells to lymph node sec-

tions via the matrix molecule vitronectin [39]. In another experimental system, adhesion of melanoma cells to intact, immobilized vitronectin induced expression of both matrix metalloprotease-2 and its inhibitor, as well as enhanced invasion by the melanoma cells [40]. These data are similar to our own finding of enhanced invasiveness following tumor cell adhesion to endothelium grown on "differentiating" acid extracts of lymph node (as opposed to lung) matrix [41]. Adhesion to generation or digestion of other known matrix molecules such as type IV collagen, fibronectin, SPARC, and tenascin has been shown to either modulate metastasis in experimental systems or correlate with metastatic spread in clinical studies [22,42–45]. Undoubtedly, there are more as yet undescribed matrix molecules that also affect the behavior of metastatic tumor cells, although none of these matrix molecules is known as being particularly abundant in lymph nodes.

Still, cell molecules that mediate adhesive interaction with matrix and with each other may be more abundant in lymph node than elsewhere. For example, there is some evidence that increased tumor cell attachment in the lymph nodes rather than growth stimulation by a cytokine-rich environment is at least partly responsible for the pattern of preferential lymph node metastasis [7]. Promotion of cell-cell adhesive interactions between T cells, B cells, and professional APCs appears to be a crucial function of the lymph node. The undifferentiated CD4 T helper cell (T_{ho}) relies on major histocompatibility complex (MHC) class II as well as T-cell receptors and, to some extent, ICAM expression to become T_{h1} or T_{h2} helper cells [46–49]. These molecules work in concert with other cell surface adhesion molecules to ensure appropriate signaling and communication between cells. T_{h2} cells promote a humoral response involving B cells and mast cell activation, while T_{h1} cells promote activation and clonal expansion of cytotoxic T cells. This differential immune response is largely dictated by the expression of cytokines. T_{h1} cells secrete cytokines such as interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-α, while T_{h2} cells secrete IL-4, IL-10, and transforming growth factor (TGF)-β. Promotion of one arm of the T helper response leads to augmentation of that arm and to suppression of the alternative arm. For example, IFN-γ promotes the T_{h1} response but inhibits T_{h2} cytokine production and thereby disables the humoral response. Expression of IL-4 and IL-10 early in the immune response will lead to T_{h2} response and inhibit cytokine production by the T_{h1} subtype which leads to a suppression of cytotoxic T-cell activation [50–52].

There do appear to be CD8+ T cells in lymph nodes that drain tumors which are capable of effecting an immune reaction against these tumor cells when the lymphocytes are expanded and stimulated ex vivo [53]. Therefore, it is reasonable to expect that enhanced expression of some adhesion molecules by tumor cells in a lymph node environment might stimulate these T cells and actually decrease the likelihood of lymph node metastasis. In fact, there is evidence that decreased ICAM-1 is associated with an increased likelihood of lymph node metastasis in non-small cell lung cancer [54]. Nevertheless, the proinflammatory cytokines involved in the T_{h1} response tend to increase both the number and the density of adhesion molecules on the surface of endothelial cells and enhance metastasis in experimental systems. ELAM and VCAM are two examples of these types of receptors and they react with two different classes of ligands: selections and integrins (especially α-4 integrin) [37,55–57]. There is a fairly extensive literature on the correlation of cell adhesion molecules on tumor cells with the likelihood of lymph node or distant metastases. However, the results of upregulation of any one type of adhesion molecule are decidedly mixed. Alpha-4 integrin expression is a good example of this problem. Some tumor cells with high numbers of these receptors are more likely to establish metastases in particular locations, especially if the target site has been treated with proinflammatory cytokines. However, in other tumor lines, successful engagement of this receptor results in apoptosis of the cells, inhibiting the ultimate formation of metastatic colonies in the organ where the cells do adhere more avidly [55].

If the impact of differential expression of cell adhesion molecules on tumor cell metastasis to lymph node is difficult to predict, then assessing the impact of cytokine production in the lymph node on metastasis formation there is purely speculative. In the lymph node, cells such as T helper, B cells, macrophage, and natural killer cells secrete combinations of more than 17 ILs and growth factors [52,53,49,58,59].

Still, an educated guess about what could be happening in the local regional lymph node draining a tumor is possible. The proinflammatory cytokine IL-1 augments lymphocyte responses and is involved in the upregulation of ICAM-1, VCAM, and E-selectin. These contribute to lymphocyte homing to the lymph node via HEVs and afferent vessels. Increases in IL-1 expression may promote tumor cell migration and adhesion to the lymph node by altering the adhesive properties of both lymphatics and lymph node. IL-2 expression increases IL-4 production except in the presence of IFN-γ. IL-4 also induces VCAM-1 expression on endothelial cells, whereas IFN-γ activates ICAM expression and inhibits IL-4 production. IFN-γ also contributes to the rich cytokine environment that maintains the function and phenotype of HEVs [4]. The consequences of this regulatory sequence are complex in the context of tumor metastasis to the lymph node. A lymph node microenvironment deficient in IFN-γ might be incapable of recruiting appropriate numbers of cytotoxic lymphocytes to the lymph node via

the IFN-γ-dependent HEVs, and result in a skewed expression of adhesion molecules such as VCAM and ICAM. Downregulation of ICAM and upregulation of VCAM could encourage successful metastasis by improving adhesion of tumor cells to endothelium and matrix without promoting an adhesive interaction with cytotoxic T cells. Alternatively, tumor cells secreting their own cytokines such as IL-4 and IL-10 could alter the lymph node environment by inhibiting cytokines such as IFN-γ. Perhaps the secretion of IL-4 and/or IL-10 by tumor cells promotes the T_{h2} immune response and subsequent inhibition of the T_{h1} response which would normally activate cytotoxic T-cell killing of tumor cells. There may even be clinical evidence that removal of lymph nodes in which a B-cell/humoral response to tumor antigens is prominent results in improved survival of colon cancer [60].

In summary, it appears that the phenomenon of preferential lymph node metastasis results from the facts that 1) the lymph node is an efficient filter for tumor cells arriving via the lymphatics, and 2) the efficiency is derived from the adhesive environment of this immunologically active site. Some of these adhesive interactions may promote tumor cell invasion and proliferation and some may provoke production of particular cytokine repertoire from the resident immune cells. As an initial approximation, one would postulate that a T_{h2} response would predominate. Subsequently, a change in the cytokine profile of the lymph node microenvironment may further encourage tumor cell growth and invasion. Whether changes in cytokine expression are a normal response to the abnormal presence of the tumor cells or tumor antigen in the lymph node, the secretion of cytokines in increasing amounts by tumor cells themselves, or both, is unknown. Still, it is reasonable to suppose that artificial manipulation of the cytokine environment of the lymph nodes draining a primary epithelial tumor may alter the subsequent metastatic ability of that tumor. These are testable hypotheses which we believe will eventually lend to a more complete understanding of how the clinical course of a human carcinoma is affected by host-tumor cell interactions in the earliest metastatic site.

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